Remarks

Claims 45 and 46 are cancelled and new claims 54-58 added. Therefore, claims 44, 47 and 53-58 are pending.

Support for new claim 54 is provided by p. 14, lines 14-15. Support for new claims 55-59 is provided by e.g., paragraph bridging pp. 47-48 and p. 15, line 12 to p. 16, line 2. New claims 55-59 are method of use claims and define the transgenic mouse used in the claims in the same manner as claim 44.

The rejections are addressed in the order made. Applicants further respectfully request that the finality of the rejection be withdrawn because at least some of the new rejections are not based on amendments made by the applicants. This issue is raised more fully below.

I. Rejection under 35 USC 112, first paragraph (written description).

Claim 46 was rejected as failing to comply with the written description requirement of the first paragraph of § 112. Although claim 46 is cancelled, rendering this rejection moot, the Examiner's comments do not appear to be specifically addressed to claim 46. Thus, in the interests of compact prosecution, the substance of the Examiner's remarks is addressed herein.

The Examiner alleges the specification does not describe an actual reduction to practice, does not describe the transgenic mice and their phenotype, does not describe any human variable gene locus. The Examiner also alleges that the skilled artisan cannot envisage the detailed chemical structure of the claimed transgenic mice (citing to *Fiers v. Revel* and *Amgen v. Chugai*). The Examiner further alleges that the skilled artisan would not recognize that applicant was in possession of the necessary common features possessed by the genus.

In reply, applicants cite MPEP 2163 which supports that an invention can be described without a reduction to practice with detailed drawings or description of identifying characteristics. The lack of a requirement for an actual reduction to practice has also been recently reemphasized by *Falkner vs. Inglis*, 79 USPQ2d 1001 (Fed. Cir. 2006) ("The Board was correct, however, not to view as dispositive that Inglis had not actually produced a poxvirus vaccine, because an actual reduction to practice is not required for written description.") Here, applicants have provided both detailed drawings and a description of identifying characteristics so an actual reduction to practice is not required. The specification and claims describe the essential physical characteristics of the claimed transgenic mice that distinguish them from other transgenic mice (i.e., human heavy and light chain variable region gene loci replace mouse endogenous heavy and light chain immunoglobulin variable region gene loci, and the human heavy and light chain variable region loci are linked to endogenous mouse heavy and light chain immunoglobulin constant region gene loci to form hybrid loci, whereby the hybrid loci rearrange during B-cell development such that the mouse

produces a serum containing an antibody comprising human heavy and light chain immunoglobulin variable regions and mouse heavy and light chain immunoglobulin constant regions in response to antigenic stimulation). The specification and claims also describe the resulting phenotype of the mice (i.e. production of chimeric antibodies). The specification also provides detailed drawings of mouse and human immunoglobulin gene loci to be combined and exemplary targeting vectors to be used in generating the mice (Figs. 4A-D). The specification also describes exemplary procedures for generating the mice (pp. 44-48). Although written description does not require reproduction of known sequences, the specification in fact provides GenBank notations for the human immunoglobulin locus (p. 45, second paragraph). No allegation is being made that these procedures cannot be practiced without undue experimentation.

The facts and circumstances underlying the present claims are considerably different than those in the cases cited by the Examiner. In *Amgen*, the claims at issue were directed to nucleic acids encoding human erythropoietin, a protein that had not hitherto been cloned. The court held that one could not conceive of such nucleic acids until they had actually been isolated and sequenced. Similarly, in *Fiddes*, the court held that one could not conceive of nucleic acids encoding human fibroblast beta interferon, another hitherto uncloned human protein, until such nucleic acids had actually been isolated and sequenced. Likewise, in *Lilly*, the court held that a claim directed to nucleic acids encoding human insulin (another hitherto uncloned human protein) lacked written description in the absence of actual sequence data for a nucleic acid encoding human insulin. The *Lilly* court also found that generic claims to cDNA encoding vertebrate or mammalian insulin lacked written description because:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definitions. It does not define any structural features commonly posses by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated does not suffice to define the genus because it is only an indication of that the gene does, rather than what it is. (43 USPQ2d at 1406).

The present claims differ from those at issue in the *Amgen*, *Fiddes* and *Lilly* cases in a number of respects.

First, the nature of the invention underlying the present claims is the provision of transgenic mice defined by reference to well characterized genomic loci (i.e., the human and mouse

immunoglobulin loci), not the discovery of a new sequence. In each of the cited cases, the invention resided in the *de novo* isolation of a gene.

Second, the present claims do not characterize the claimed transgenic mice only by function but by reference to the genomic modification that distinguishes the claimed mice from nontransgenic mice and other types of transgenic mice. Thus, the claimed mice are defined by "structural features commonly possessed by members of the genus that distinguish them from others." Because the human and mouse immunoglobulin loci are well-characterized, this description is sufficient to envisage the claimed mice, and to determine whether any mice of interest meets the claimed requirements.

This situation is distinct from that in the cited cases in which the claims were directed to a DNA molecule encoding a hitherto uncloned human protein and one had no meaningful way of describing or recognizing this molecule without its sequence being determined. Because the facts and circumstances of *Amgen*, *Fiddes* and *Lilly* are entirely different from the present, these cases do not support the view that the present claims cannot be described without a reduction to practice. Accordingly, it is respectfully requested that this rejection be withdrawn.

II. Rejection under 35 USC 102(e).

A. The Examiner repeated the rejection of claims 44-47 as anticipated by Jakobovits et al. (US 6,130,364). Claims 45-46 are cancelled. This rejection is respectfully traversed as it may be applied against claims 44 and 47.

Regarding the Examiner's cite to Jakobovits et al., col. 6, lines 34-49, it is respectfully pointed out that Jakobovits et al. teach modification of the genome of hybridomas, that is, cells in which the variable immunoglobulin regions are already rearranged. The Examiner's statement that Jakobovits et al. teach the creation of transgenic mouse comprising a genetically modified immunoglobulin variable region gene locus is not correct. Jakobovits et al. teach a transgenic mouse having a lox site inserted 5' of the immunoglobulin locus. While this is a "modification", it is not the modification encompassed by the instant invention. Rather than teaching a transgenic mouse, Jakobovits et al. actually teach the creation of an antibody producing cell comprising a genomically modified immunoglobulin locus.

In regard to the Examiner's cite of Jakobovits et al. at col. 7, lines 36-45, the modification taught by Jakobovits et al. is integration of a lox site. Jakobovits et al. teaches introducing a lox site into a transgenic mouse with a transgene encoding human immunoglobulin genes as a means of facilitating modification of hybridomas derived from such a mouse. The modification of the genome of such mice to introduce a lox site is unrelated to that of the claimed mice in which human heavy and light chain variable region loci are operably linked to endogenous mouse heavy and light chain

immunoglobulin constant region gene loci to form hybrid loci, and the hybrid loci rearrange during B-cell development such that the mouse produces chimeric antibodies.

Applicants respectfully point out that a source of the Examiner's confusion is the reference in Jakobovits et al. of DNA "encoding the variable region of an antibody" with a unique specificity. This is not the same as the "variable region locus" referred to in the instant claims, which contain unrearranged germline V, D and J segments, and which can be rearranged in the mouse during B cell development to give rise to a plethora of different antibody specificities.

Further, Applicants respectfully point out that Jakobovits et al. do not teach a mouse in which the mouse variable genome is replaced with the human sequence, they teach replacement of the variable region of an antibody in an antibody expressing cell.

In light of the above remarks, it is respectfully requested that this rejection be withdrawn.

B. Claims 44-47 and 53 were rejected as lacking novelty over Lonberg et al. (US 5,877,397). Claims 45-46 are cancelled. This rejection is respectfully traversed.

Lonberg is cited as teaching transgenic mice in which human immunoglobulin genes are introduced into the mouse Ig locus by replacing mouse heavy and light immunoglobulin loci with human heavy and light chain loci using homologous recombination (citing to cols. 31-74). The Examiner alleges Lonberg teaches a genomic heavy chain transgene at col. 31, a genomic light chain formed by homologous recombination at col. 32 and functionally rearranged variable region sequences in B cells (at col. 70).

The cited Lonberg et al. reference. Contrary to the Examiner's characterization of the Lonberg et al. reference, it is respectfully pointed out that Lonberg et al. in fact describe a method of generating transgenic mice which involves inactivating mouse endogenous loci and introducing human immunoglobulin loci as two separate processes.

In such an approach, the human immunoglobulin loci would enter the mouse genome at random locations rather than at the mouse loci. Such a transgenic mouse would have inactivated mouse immunoglobulin loci and functional human immunoglobulin loci and produce fully human antibodies.

The steps for inactivating mouse immunoglobulin loci are discussed in Examples 9 and 10 of Lonberg et al. The separate steps for introducing human immunoglobulin loci are discussed in Examples 14 and 15. The homologous recombination referred to by the Examiner is not between human and mouse immunoglobulin loci, but rather between two parts of the human immunoglobulin light chain (see Example 3). Homologous recombination is also discussed in Examples 9 and 10 in connection with inactivating endogenous mouse loci. However, this homologous recombination is performed using a targeting vector containing mouse sequences flanking a selectable marker. The

effect of the recombination is to introduce a marker into the endogenous mouse locus rather than a human immunoglobulin locus.

The analysis required by § 102. For the reasons stated above, the human heavy and light chain variable region loci introduced into mice generated via the Lonberg et al. method do not replace mouse endogenous heavy and light chain immunoglobulin variable region gene loci, much less form hybrid loci with them as required by the instant claims.

Accordingly, in light of the above remarks, it is respectfully requested that this rejection be withdrawn.

C. Claims 44-47 and 53 were rejected as anticipated by Kuncherlapati, US 6,114,598. Claims 45-46 are cancelled. This rejection is respectfully traversed.

Kuncherlapati is alleged to teach transgenic mice in which human immunoglobulin genes are introduced into the mouse immunoglobulin locus by replacing mouse heavy and light chain immunoglobulin loci (citing to col. 38, lines 23-26, col. 25, lines 16-23 and col. 22, lines 1-10). The Examiner also alleges that Kuncherlapati teaches transgenic mice producing human monoclonal antibodies in response to immunization (citing to col. 39 and col. 40).

At col. 6, lines 4-38, Kuncherlapati sets forth two alternative strategies for producing human antibodies. The first strategy discussed at col. 6, line 4 to 29 is essentially the same as Lonberg et al. strategy discussed above. Endogenous loci are inactivated and human loci are introduced as two separate processes. Separate strains with inactivated loci and introduced human loci are then mated to yield animals whose antibody production is "purely xenogeneic, e.g., human" (col. 6, lines 25-30). Example I-VI of Kuncherlapati provide experimental detail of this strategy. This strategy does not anticipate the present claims for the same reasons discussed in connection with Lonberg.

The second alternative strategy is set forth at col. 6, lines 30-38) and Example VII. This strategy proposes using human immunoglobulin loci to replace and inactivate mouse endogenous loci in a single step. However, Kuncherlapati does not disclose linking human heavy and light chain variable region loci to endogenous mouse heavy and light chain immunoglobulin constant region gene loci to form hybrid loci, whereby the hybrid loci rearrange during B-cell development to produce a chimeric antibody, as claimed. To the contrary, Fig. 16C of Kuncherlapati shows the heavy chain variable region locus linked to a human constant region locus (i.e., cμ and cΔ), and separated from residual mouse genes by a neo transcriptional unit, a known inhibitor of trans switching of a variable region from one constant region to another (see Seidl et al., PNAS 96, 300-3005, 1999). No details of a light chain locus are provided at all, much less a description of a human immunoglobulin light chain variable region locus linked to a mouse constant region locus such that hybrid locus can rearrange to produce a chimeric antibody as claimed. Use of an

analogous strategy for the light chain as the heavy chain (i.e., juxtaposition of a human immunoglobulin light chain variable region locus to a human light chain constant region locus) would be still less likely to result in a chimeric light chain than a chimeric heavy chain because trans-switching is a heavy-chain-only phenomenon (see, e.g., Paul, Immunology, 2nd Edition. Ch. 22).

The goal of the second alternative strategy is the same as that of the first strategy described by Kuncherlapati, namely to produce human antibodies. Such can be inferred by juxtaposition of a human variable region locus with a human constant region locus in Fig. 16C as discussed above, and by the fact that Example VII is characterized as being "alternative approach to that set forth in Example I-VI," whose goal is also to produce fully human antibodies. There is no mention of producing chimeric antibodies in the entire Kuncherlapati patent (chimeric animals are mentioned; however, this designation simply means an animal having some but not all cells containing a transgene and does not imply that the animal produces a chimeric antibody).

"Anticipation is established only when a single prior art reference discloses, expressly or under principles of inherency, each and every element of a claimed invention," *RCA Corp v. Applied Digital Data Sys. Inc.,* 2212 USPQ 385, 388 (Fed. Cir. 1984). However, "[i]nherency ... *may not be established by probabilities or possibilities.*" *Mehl/Biophile v. Milgraum,* 52 USPQ2d 1303, 1305 (Fed. Cir. 1999) (emphasis supplied). "The mere fact that a certain thing *may* result from a given set of circumstances *is not sufficient* to establish inherency." *In re Rijckaert*, 28 USPQ2d 1955 (Fed. Cir. 1993) (emphasis supplied).

Here, it cannot reasonably be disputed that there is no express disclosure of producing chimeric antibodies or of linking human heavy and light chain variable region loci to mouse heavy and light chain constant region loci to do so. As discussed above, the heavy chain locus shown in Fig. 16C of Kuncherlapati appears designed to express human heavy chains rather than chimeric antibodies. No description of a light chain locus is provided and no mouse were actually made. Given the lack of express teaching and these uncertainties, no case of inherency can be made either.

New claim 54 is further distinguished from Kuncherlapati in that the heavy chain immunoglobulin constant region locus shown in Fig. 16C is not entirely mouse.

New claims 55-58 are further distinguished from Kuncherlapati in that they require preparing a hybridoma expressing the chimeric antibody from the mouse. As noted above, Kuncherlapati provides no mention of chimeric antibodies, much less a teaching to isolate a hybridoma expressing one. New claim 59 is further distinguished for a similar reason. Kuncherlapati provides no teaching to isolate DNA encoding the variable regions of a chimeric antibody from a transgenic mouse or to link them to DNA encoding human constant regions.

Accordingly, in light of the above remarks, it is respectfully requested that this rejection be withdrawn.

III. Withdrawal of finality

Applicants request that the finality of the rejection be withdrawn because at least some of the new rejections are not based on any amendment made by applicants. In particular, the new rejection for lack of written description appears to be based on the disclosure of the specification and is unrelated to any change of wording of the claims. It is also not apparent that either of the new art rejections are related to changes in claim wording introduced in the last response.

Conclusion

It is believed that this document is fully responsive to the FINAL rejection issued 9 August 2006. In light of the above amendments and remarks, it is believed that the claims are now in condition for allowance, and such action is respectfully urged.

Fees

The Office action is dated 9 Aug 2006 and provides a 3 month response period. This response is filed 10 October 2006, 2 months of the filing date as 9 Oct 2006 is a Federal holiday (Columbus Day). Therefore, no fee is necessary in connection with the filing of this response. If a fee is determined to be due, authorization is hereby given to charge such a fee, to Deposit Account No. 18-0650.

Respectfully submitted,

Valeta Gregg, Ph.D., Reg. No. 35,127
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, New York 10591
direct: 914-593-1077